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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,776	01/25/2002	Kurt Berlin	81796	9632

7590 11/23/2005

KRIEGSMAN & KRIEGSMAN
665 Franklin Street
Framingham, MA 01702

EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,776	BERLIN, KURT	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on August 24, 2005.

Preliminary Remark

The present Office Action contains at least a new rejection or a new objection not necessitated by Amendment, and is therefore made **Non-Final**.

Claim Rejections - 35 USC § 112 – New Grounds

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite for reciting the phrase, "[t]he method according to claim 1...whereby the immobilized oligomers hybridize at least one of the primers used in the amplification step."

There is insufficient antecedent basis for the term, "primers" in neither claim 2 nor in parent claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-3, 6-10, 12, and 13 under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

The Rejection:

Gonzalgo et al. disclose a method of fluorescently detecting the methylated cytosine in a genomic DNA sample, wherein the genomic DNA is first treated with a bisulfite (page 4, line 15; claim limitation 6), the DNA amplified by PCR or polymerase chain reaction, incorporating radioactively labeled dNTPs, such as dCTP and dGTP (page 7-8; claim limitation 7), amplicons separated via electrophoresis (page 5, line 24; claim limitation 3), and the amplicons detected radioactively (page 4, lines 10-30) or fluorescently (page 8, lines 30-31; claim limitation 12). Gonzolago et al. also disclose a method of detecting the methylated cytosine, wherein the amplicons are transferred onto a nylon membrane for dot-blot analysis (page 8, lines 34-35; claim limitation 2 and 10).

Gonzalgo et al., while employing radioactively labeled dNTPs in the amplification step, do not employ fluorescently labeled dNTPs.

Gonzalgo et al. do not employ the differentially labeled fluorescently labeled NTPs comprising cy3 and cy5.

Yurov et al. disclose the use of multicolor fluorecent detection via use of cyanine dyes, more specifically cy3 and cy5 (page 391, 1st column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gonzalgo et al. with the teachings and suggestions of Yurov et al. to arrive at the invention as claimed for the following reasons.

Although Gonzalgo et al. employ radioactively labeled dNTPs and not fluorescently labeled dNTPs, particularly cy3 and cy5 labeled dNTPs, Gonzalgo et al. acknowledges alternate ways of labeling nucleotides (*i.e.* – fluorescent labels; see page 8, lines 30-31).

In addition to this acknowledgement, Yurov et al. disclose an explicit benefit provided by the use of cy3 and cy5 dye over the traditional fluorescent labels:

"Cyanine dyes are also useful as fluorescent labels or biological macromolecules. Cyanine 3 dye provides significantly ***brigher*** fluorescence than any other fluorophore, including fluorescein..." (page 391, 1st column).

Yurov et al. also disclose the advantage of using cy3 and cy5 dyes for multicolor detection assays (page 391, 2nd column).

Additionally, it is an art-recognized advantage that the use of fluorescent labels are environmentally safer as well as more efficient.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to take the suggestion of Gonzalgo et al. and the advantage offered by Yurov et al. as well as art-recognized advantage of using fluorescent labels over the radioactive labels to arrive at the claimed invention. Since the substitution of fluorescently labeled nucleotides have been well established in the art of nucleic acid amplification and detection as evidenced by Davis et al.:

"Amplified sequences can be labeled by, for example, incorporation of a labeled nucleotides (e.g., a fluorescent nucleotides such as Cy3-dUTP or Cy5-dUTP, or a radioactive nucleotide" (Davis et al., at column 19, lines 18-20)

One of ordinary skill in the art would have had a clear expectation of success at substituting the radioactive labeling with fluorescent labels provided by Yurov et al.

Response to Arguments:

Applicants traverse the present rejection. Applicants' traversal is drawn to the independent claim 1, which has been amended to include step (e), reciting the phrase, "then, determining from the measured fluorescence the relative number of methylated cytosine bases that were present in the DNA sample prior to step a)," step (a) being drawn to the treatment of a genomic DNA sample with a reagent, wherein 5-methylcytosine and cytosine react differently (page 6, bottom, Response). The preferred embodiment of such reagent is a bisulfite solution which converts unmethylated cytosine to uracil (see claim 6).

Applicants contend that Gonzalgo et al. does not relate to a method for determining the relative number of methylated cytosine bases in a DNA sample, but rather, is directed at a method for determining whether or not a cytosine at a particular location is methylated (page 7, bottom paragraph, Response).

This argument is not found persuasive for the following reasons.

The method disclosed by Gonzalgo et al. employs the treatment of a genomic DNA sample with a bisulfite solution, which results in the conversion of unmethylated cytosine residues to uracil residues while not changing the 5'methylated cytosine residues. This step is the same as step (a) of instant claim 1. The resulting DNA sample is then amplified via PCR with primers specific for bisulfite-converted DNA, followed by the electrophoresis of the amplified product. Applicants appear to be of the assumption that this is step is what is relied on by the Examiner in meeting the limitation of step (b) and (c). This assumption, however, is not correct. Gonzalgo et al. takes the amplified product (which contains the chemically reacted DNA sample therein), and conducts

SNuPE on the amplified product (see Figure 1). The SNuPE involves the hybridization of a primer to the nucleic acids of the amplified product, followed by its extension with at least labeled dCTP and dGTP (see page 8, lines 6-8). By the extension reaction, the products are "amplified," followed by the separation of the amplified products on a denaturing polyacrylamide gel (page 8, lines 31-34) via electrophoresis, thereby fully meeting step (b) which amplifies via use of labeled dCTP and dGTP; step (c) which spatially separates the amplified product (via electrophoresis).

Gonzalgo et al. disclose that the relative quantification of the methylation is determined (page 8, lines 29-28). The methylation detection disclosed by Gonzalgo et al. is drawn to the methylation of 5-methyalcytosine. Hence, the relative quantification of the methylation would be that of the cytosine, thereby meeting steps (d) and (e) of claim 1.

Applicants contend that the method of Gonzalgo et al. is directed at a method for determining whether or not a cytosine at a particular location is methylated (page 7, bottom paragraph, Response). Applicants' attention is drawn to the section of the disclosure of Gonzalgo et al. which discusses that the methylation "at each CpG site" is determined (page 8, lines 28-29), as well as CpG island (page 7, lines 35-36; page 9, lines 32) using multiple SNuPE primers, resulting in the detection of each of methylated cytosines on the CpG island, resulting in the determination of the relative number of methylated cytosine bases. With regard to argument drawn to the method of Gonzalgo et al. being drawn to determining the methylation of cytosine at a particular location, the method as claimed clearly embraces the method disclosed by Gonzalgo et al., with the exception of using fluorescently labeled nucleotides. In addition, the instant specification discloses that "specific primers", MRP3 and MDR1 were employed in an amplification step involving the incorporation of Cy5-dCTP, amplifying a specific region (thus a particular location; page 18, example 3).

With regard to the arguments drawn to the claimed method being drawn to determining "relative number of cytosine methylations," (page 8, bottom paragraph, Response) the method of Gonzalgo et al. determines the number of cytosine methylation relative to the unmethylated cytosines on the DNA strand.

Applicants also contend that the method of the instant application can be used in determining the presence and extent of "co-methylation," a biological phenomenon in which a majority of CpG locations within CpG rich region share the same methylation status (page 8, bottom paragraph). This argument is not found persuasive because the claims are not drawn to this method. In addition, Gonzalgo et al. disclose a multiplex primer strategy (page 7, line 35-36) which allows the determination of many CpG sites.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Gonzalgo et al. with the teachings of Yurov et al. in employing fluorescently labeled nucleotides for the well-known advantage of employing biologically safer material as well as employing labels which produce stronger signals, with a reasonable expectation of success, as evidenced by Davis et al., rendering the invention as claimed *prima facie* obvious over the cited references.

The rejection of claims 4 and 5 under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), as applied to claims 1-3, 6-10, 12, and 13 above, and further in view of Apffel et al. (U.S. Patent No. 6,379,889 B1, issued April 30, 2002, filed November 4, 1999) and Roche et al.

(Biotechnology Progress, 1997, vol. 13, pages 659-668), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

All of Applicants' arguments are drawn to claim 1 (as amended) and whether said claim is patentable over the art of record. As already discussed above, claim 1 not patentable over the cited references, and as Applicants lack additional arguments as to why claims 4 and 5 are patentable over the references of record, the present rejection is maintained for the reasons of record.

The rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), as applied to claim 1 above, and further in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

All of Applicants' arguments are drawn to claim 1 (as amended) and whether said claim is patentable over the art of record. As already discussed above, claim 1 not patentable over the cited references, and as Applicants lack additional arguments as to why claim 11 is patentable over the references of record, the present rejection is maintained for the reasons of record.

The rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

Applicants contend that the Office has failed to give any weight to the fact that "consisting" of is used instead of comprising (page 13, Response). Applicants contend that the Office has to explain why one of ordinary skill in the art would have been motivated to make all of the modifications needed to change the Gonzalgo method to the claimed method, including the elimination of the primer extension step.

It is respectfully pointed out that SNuPE step involves the "extension" of the primer, resulting in the amplification of the template nucleic acids. In addition, so long as the prior art reference does not teach away from the claimed modification, one of ordinary skill in the art would be motivated to make various modifications of the methods so as to arrive at the claimed invention. In other words, a method consisting of steps: a) isolating DNA from a sample; b) hybridizing a target oligonucleotide probe complementary to a target nucleic acid; and c) detecting the presence of the target nucleic acid; would not be unobvious over a prior art reference teaching a method of steps: a) isolating DNA from a sample; b) amplifying a target nucleic acid via primers; c) hybridizing a target oligonucleotide probe complementary to a target nucleic acid; and d) detecting the presence of the target nucleic acid; solely based on the rationale that the method as claimed is "consisting of." Similarly, so long as the prior art reference does not teach away from the claimed method, it would

be obvious to one of ordinary skill in the art to combine the teaching steps as necessary to arrive at the claimed invention, render the invention as claimed obvious over the cited references.

The rejection is maintained therefore.

Double Patenting – Maintained

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/220,090 (herein the '090 application), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

Applicants contend that claims 1-29 of the '090 application does not teach the step of determining from the measured fluorescence the relative number of methylated cytosine bases that were present in DNA sample prior to step (a) as iterated in claim 1 step (e) of the present application.

Claim 1 of the '090 application recites the below steps:

(a) a genomic DNA from a DNA sample is chemically converted with a reagent, 5-methylcytosine and cytosine reacting differently (identical to claim 1 (a) of the present application);

(b) the pretreated DNA is amplified using a polymerase and at least one primer, and the amplified product (which also contains the pretreated DNA) is hybridized to a primer, wherein upon hybridization, the primer is extended via means of a polymerase with a plurality of labeled nucleotides (steps c and d of the '090 application), wherein the label is further recited as being fluorescent labels (claim 12 of the '090 application).

The extension of the primer via the fluorescently labeled nucleotides would result in an increase in the DNA molecules (thus amplification). The incorporation of the fluorescently labeled nucleotides would necessarily result in the quantification of the methylated cytosine residues, rendering claim 1 obvious over claims of the '090 application.

Applicants are also advised that claims 14-15 of the '090 application also recites the step of mass spectrometer detection, which also involves spatial separation of the amplified products.

The rejection is maintained therefore.

The rejection of claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/220,896 (herein the '896 application), made in the Office Action mailed on March 1, 2005 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Applicants' arguments presented in the Amendment received on August 24, 2005 have been fully considered but they are not found persuasive for the following reasons.

Applicants state that for the "same types of reasons," (as above) the rejection should be withdrawn.

The argument was that claims 1-29 of the '896 application does not teach the step of determining from the measured fluorescence the relative number of methylated cytosine bases that were present in DNA sample prior to step (a) as iterated in claim 1 step (e) of the present application.

Claim 1 of the '896 application recites the below steps:

(a) a genomic DNA from a DNA sample is chemically converted with a reagent, 5-methylcytosine and cytosine reacting differently (identical to claim 1 (a) of the present application);

(b) the pretreated DNA is amplified using a polymerase and at least one primer, and the amplified product (which also contains the pretreated DNA) is hybridized to a primer, wherein upon hybridization, the primer is extended via means of a polymerase with a plurality of labeled nucleotides (steps c and d of the '896 application), wherein the label is further recited as being fluorescent labels (claim 12 of the '896 application).

The extension of the primer via the fluorescently labeled nucleotides would result in an increase in the DNA molecules (thus amplification). The incorporation of the fluorescently labeled nucleotides would necessarily result in the quantification of the methylated cytosine residues, rendering claim 1 obvious over claims of the '896 application.

Applicants are also advised that claims 14-15 of the '896 application also recites the step of mass spectrometer detection, which also involves spatial separation of the amplified products.

The rejection is maintained therefore.

Applicants are advised that with regard to provisional obviousness-type double patenting rejection, MPEP 804(I)(B) instructs as below:

> "If the "provisional" double patenting rejections in both applications ***are the only rejections remaining*** in those applications, the examiner should then ***withdraw that rejection*** in one of the applications (e.g., ***the application with the earlier filing date***) and permit the application ***to issue*** as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented."

The instant application has a rejection that is substantive other than the provisional double patenting rejections, and are therefore, maintained.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be

sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
11/21/2005

YOUNG J. KIM
PATENT EXAMINER

yjk